Kidney International, Vol. 66, Supplement 92 (2004), pp. S99–S101

Impact of irbesartan, blood pressure control, and proteinuria on renal outcomes in the Irbesartan Diabetic Nephropathy Trial

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Background. It is important to know the reliability of early changes in proteinuria in predicting late renal outcomes. The IDNT was a trial in which treatment assignment, baseline and follow-up blood pressure determinations, and albumin/creatinine ratios (ACR), and renal outcomes were recorded.

Methods. Risk of renal outcomes in the IDNT was assessed by proportional hazards modeling as a function of treatment assignment, and achieved systolic blood pressure (SBP) both without, and then with, inclusion of values for baseline proteinuria and early changes in proteinuria.

Results. In models without ACR variables, both treatment with irbesartan and achieved SBP during follow-up were significantly predictive of the risk of renal outcomes. Addition of ACR variables to the models reduced the apparent impact of assignment to irbesartan by 52% to 81%, and irbesartan was no longer a significant predictor of renal outcomes. Conversely, addition of ACR variables to the models attenuated the effect of achieved follow-up SBP by only 32% to 46%, and follow-up BP remained a highly significant predictor of renal outcomes.

Conclusion. The ability of early changes in proteinuria to predict the impact of treatment on renal outcomes is a function of the specific treatment. One must use caution in using early changes in proteinuria as a surrogate for longer-term renal outcomes.

The Irbesartan Diabetic Nephropathy Trial (IDNT) was a multinational, multicenter, randomized, double-blinded, placebo-controlled trial designed to determine the impact of treatment with the angiotensin II receptor blocker irbesartan (compared with amlodipine and placebo) on renal and cardiovascular outcomes in patients with type 2 diabetic nephropathy. The methods and major renal and cardiovascular outcomes have been reported [1–3]. We have previously reported that both treatment with irbesartan and achievement of a lower follow-up systolic blood pressure (SBP) were independently associated with improved renal outcomes [2, 4]. We have also reported that both irbesartan treatment and lower blood pressure were associated with a reduction in proteinuria [5]. The present paper examines the extent with which the beneficial effects of irbesartan treatment and lower achieved SBP were correlated, and could be predicted by, their effects to reduce proteinuria.

Key words: albuminuria, ESRD.

METHODS

The general methods of the IDNT and the methods for ascertaining outcomes have previously been detailed [1, 2]. For the purposes of this study, a renal outcome was the composite of either doubling of serum creatinine or development of end-stage renal disease (ESRD), which ever was earlier. Blood pressure was measured twice prior to randomization and at quarterly visits thereafter. Blood pressure declined on average by 15 mm Hg from baseline to six months, and was fairly stable thereafter. Therefore, mean follow-up SBP was defined as the mean of values obtained at all quarterly study visits on or after six months. Twenty-four–hour urines were collected twice during baseline, at three and six months, and every six months thereafter. Albumin and creatinine values were determined centrally. An albumin/creatinine ratio (ACR) was computed from these 24-hour urines. The values for the ACR were log transformed to approximate a normal distribution. Among patients assigned to irbesartan, proteinuria declined sharply over the first three to six months [5], whereas proteinuria among patients assigned to amlodipine or placebo changed little. After six months, proteinuria in all groups declined slowly for the remainder of the study. Therefore, average follow-up proteinuria was defined as the mean of the log-transformed ACR from six months to the end of the study. The impact of treatment assignment and of baseline and mean follow-up SBP and ACR on patients with renal survival for at least six months was determined by proportional hazards analysis of the time to the composite renal outcome, as defined above.

Table 1. Impact of various factors on risk of a renal event in the IDNT

Factor	Relative risk	95% CI	*P* value
Model 1			
Irb vs. Aml or Plac	0.69	0.56–0.85	0.0007
15 mm lower fu SBP	0.63	0.56–0.70	<0.0001
Model 2			
Baseline log2(ACR)[a]	3.15	2.79–3.85	<0.0001
Δ log2(ACR) B-6mo[b]	0.41	0.36–0.47	<0.0001
Model 3			
Irb vs. Aml or Plac	0.85	0.68–1.07	0.17
15 mm lower fu SBP	0.80	0.72–0.90	0.0001
Baseline log2(ACR)[a]	3.07	2.71–3.47	<0.0001
Δ log2(ACR) B-6mo[b]	0.42	0.37–0.49	<0.0001

[a]For each doubling of ACR.
[b]For each halving of ACR.

RESULTS

We have previously reported that treatment with irbesartan (compared with either amlodipine or placebo) and a lower follow-up SBP were independently significantly associated with an improved renal outcome [4]. These effects are listed as Model 1 in Table 1. We have also previously reported that both baseline proteinuria and the change in proteinuria during follow-up are strong independent predictors of the renal outcome [5]. These effects are listed as Model 2 in Table 1. Finally, we have reported that both treatment with irbesartan and a lower achieved SBP independently reduced the ACR [5]. Treatment with irbesartan led to a 47% (95%CI 39–53, $P < 0.0001$) reduction of follow-up ACR compared with amlodipine or placebo, while a 15 mm Hg lower follow-up SBP was associated with a 18% (95%CI 12–23, $P < 0.0001$) reduction in the ACR.

Since treatment with irbesartan and a lower achieved follow-up SBP both lower proteinuria and protect against the renal end point, it is of interest to see whether the effects of either treatment with irbesartan or lower achieved SBP can be "explained" by the reduction in ACR. This can be tested by putting all four factors into the same renal survival model. The results of this analysis are shown as Model 3 in Table 1. It can be seen in this model that addition of treatment and follow-up blood pressure has very little effect on the impacts of baseline and follow-up changes in ACR, but that inclusion of the ACR variables attenuates the impact of treatment by 52%, and of achieved SBP by 46%. Treatment with irbesartan is no longer a significant predictor of outcomes, but lower SBP remains highly significantly associated with a better renal outcome, independent of the ACR variables. If one includes three-month values for proteinuria and SBP into the models, the impact of irbesartan treatment (RR 0.94, 95%CI 0.74–1.19, $P = 0.61$) is further attenuated to 19% of its value prior to adjustment for proteinuria, while the impact of follow-up SBP (RR/15 mm Hg 0.75; 95%CI 0.67–0.85, $P < 0.0001$) is restored to 68% of its value prior to adjustment for proteinuria.

DISCUSSION

There remains controversy about the extent to which early changes in proteinuria predict reliably the long-term impacts of interventions to preserve renal function in renal disease. It is clear that initial proteinuria is a strong predictor of renal outcomes, and that early reductions in proteinuria generally indicate an improvement in outcomes. The results of the analyses above are consistent with many other reports, including several in this supplement, suggesting that the beneficial impact of blockade of the renin-angiotensin-aldosterone system (RAAS), as by an agent such as irbesartan, is strongly correlated with early changes in proteinuria. But this relationship may not hold for other interventions. Specifically, the beneficial impact of blood pressure reduction is not closely correlated with early reductions in proteinuria. The above results show that a lower achieved SBP during follow-up remains an important and highly significant predictor of renal outcomes, independent of baseline and follow-up proteinuria. These results are consistent with an analysis from the Modification of Diet in Renal Disease Study, showing that early changes in proteinuria accounted for only about 20% of the impact of random assignment to the lower blood pressure group [6]. Conversely, the results of the African American Study of Kidney Disease [7] have shown that assignment to the lower blood pressure arm of the study, though associated with a significant reduction in proteinuria, was associated with no protection against the renal outcomes. This would seem to imply that one should use considerable caution in assuming that early changes in proteinuria will reliably predict the later outcomes of interventions, at least those other than RAAS blockade.

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